pathogens selected from the group consisting of hepatitis C, hepatitis delta, yellow fever, dengue hemoragic fever, tetanus, staphylococcus aureous, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever (listed in claim 3 only). Since the specific NEP's are not listed in Claim 1, to which the rejection applies, it is assumed that the Examiner is applying the rejection to the NEPA language in general. Since this language was in original Claim 1, the rejection can in no way be considered necessary as a result of any amendment made by the Applicants.

The addition of this group of examples of non-enteric pathogens to claim 3 narrows the original claim ; therefore, a rejection based upon non-enablement should have been made in the original rejection. The amendment of the prior claims by the Applicants did not make the present rejection necessary. If the rejection were proper, it clearly would have been even more proper against the original claims.

In any case the rejection should be withdrawn since there is in fact clear enabling support in the specification.

The Examiner has said on page 12 that "Arntzen teaches methods of making a transgenic plant expressing an immunogen derived from Hepatitis B surface antigen...." and on page 14 "Stites teaches on page 724, Column 2, lines 1-42, the principles of "booster" reimmunization in a previously immune or "immunoreceptive" individual. The Examiner further says on page 13 of the official action, "... Koprowski as taught above teaches plant infecting microorganisms and solanaceous plants, including potatoes used to express non-enteric pathogens." On page 14, the Examiner says, "Thus it would have been obvious to one skilled in the art at the time the invention was made to provide a secondary immune response to a non-enteric pathogen in a

mammal and/or human which was made immunoreceptive by vaccination by feeding the individual transgenic plant material expressing a non-enteric pathogen antigen because Stites teaches on page 724, Column 2, lines 1-42, the principles of "booster" reimmunization in a previously immune or "immunoreceptive" individual.

It is difficult to reconcile the above statements and allegations of the Examiner with a position that the present application does not provide enablement. Enablement must be considered in light of knowledge available to one skilled in the art, including the teachings of the references cited by the Examiner. This is especially true since a number of prior art documents, including cited Arntzen patent 5,914,123, have been incorporated by reference. Almost the entire Arntzen patent teaches how numerous plants can be genetically transformed to encode foreign genes and specifically teaches incorporation of antigens for poliomyelitis, measles, mumps, rubella, smallpox, yellow fever, hepatitis B, influenza, rabies, adenoviruses, Japanese b encephalitis, varicella, parvovirus, feline leukemia, etc. Similar teachings are given in the other patents incorporated by reference. **There is therefore more than sufficient teaching for making a transgenic potato required for use in accordance with the present invention as broadly as claimed and it is also clearly taught that the antigens made by such potatoes can function as vaccines when separated from the plant material and injected.**

What is not suggested in the cited art is how to make such transgenic plants orally function as vaccines and that is clearly taught in the present application, i.e. use a transgenic potato expressing a non-enteric pathogen antigen as a booster after primary immunization by injection. ***The invention is thus clearly enabled.***

The Examiner has rejected Claims 1-19 under 35 U.S.C.112 as being indefinite. With due respect to the Examiner, we disagree. The claims are completely clear and have apparently been understood by the Examiner. In most instances, the alternative language suggested by the Examiner has been adopted by amendment. The phrase "enteric immune response" not been changed by deletion of "enteric" as that would have changed the clear meaning and intent of the phrase. There is no doubt that "enteric" is an adjective meaning "pertaining to the intestinal tract". See e.g. the well known "Taber's Cyclopedic Medical Dictionary", 1977. There is further no ambiguity with respect to the meaning of "immune response". An "enteric immune response" is therefore clearly an immune response that occurs in the intestinal tract. There is no ambiguity.

The generic objection is not understood. To the knowledge of the Attorney for the Applicants, the claims in fact do conform to U.S. practice and are not indefinite. The Examiner's reference to "narrative" is not understood. The claims are in the form of descriptive sentences as required. Further, to the knowledge of the Attorney for the Applicants, there are no grammatical or idiomatic errors and the Examiner has pointed to none. The objection is therefore improper and should be withdrawn.

Claims 1-19 have been rejected under 35 U.S.C. 103 as being unpatentable over Koprowski et al. (A), in view of Stites et al. (U).

The Examiner states that Koprowski "teaches a method of providing an immune response in a mammal and/or human to a non-enteric pathogen, especially the non-enteric pathogen rabies street virus. In the process, a physiologically acceptable plant is genetically altered to express an

antigen." Despite the Examiner's assertions, **Koprowski at al. does not teach or suggest any method for making a transgenic plant as required by the present claims nor a method for using such a plant to obtain an immune response.** Koprowski et al. instead teaches a microorganism expressing a bioactive compound, e.g. an immunogenic rabies polypeptide. The microorganism may then be used to infect a plant as a parasite but does not alter the genetic character or expression of the plant. Furthermore, rabies should not be considered a non-enteric pathogen since it can sometimes invade or attack enterically.

Koprowski et al. suggest that their method has wide application, e.g. for treatment of viral infections, bacterial infections, fungal infections, protozoan infections, diabetes, immune disorders, cancer and heart disease. Kaprowski et al. more specifically suggest that their method could be used for mucosal pathogens, e.g. rabies, respiratory syncytial virus, cholera. typhoid fever, herpes simplex types I and II, tuberculosis, pathogenic pneumococci, human immunodeficiency virus-1 (HIV-1) and human immunodeficiency virus-2 (HIV-2).

The only specific example given is for rabies which is not considered a non-enteric pathogen in accordance with the present invention since it can invade enterically. There is no enablement for the other suggested applications. If the disclosure actually enabled everything suggested, oral vaccines effective against Aids, cancer, and herpes, among many others, would be made available simply by following the teachings of the Kaprowski et al patent. It is well known that this is not the case.

Kaprowski et al. certainly does not enable or even reasonably suggest application for orally raising an immune response to an antigen by feeding a transgenic plant. Koprowski et al.

does not suggest using any kind of plant material to obtain a secondary immune response. There is certainly no suggestion of feeding a potato expressing an antigen for an NEP, after immunization by injection, to obtain a secondary immune response.

Stites et al. adds nothing to cure the inadequate teachings and suggestions of Kaprowski et al. Stites et al. does not suggest anything concerning orally raising an immune response to an antigen expressed by a plant. Further, Stites et al. clearly does not suggest any method for **orally** raising a highly effective secondary immune response by feeding a potato expressing an antigen after prior injection of the antigen.

The rejection is therefore clearly improper and should be withdrawn.

Claims 1-19 have been rejected under 35 U.S.C. 103 as being unpatentable over Arntzen et al. and Koprowski et al. in view of Stites et al.

This rejection is similar to the rejection above with the further addition of the Arntzen et al. patent.

Arntzen et al. does nothing to cure the critical defects of the Koprowski et al and Stites et al. references.

Arntzen et al. teaches a method for making a transgenic tobacco, tomato or potato that expresses HBsAg.

Notwithstanding the Examiner's assertion, **Arntzen et al. does not teach "methods of making a transgenic plant expressing an immunogen derived from hepatitis B surface antigen, wherein the immunogen is capable of eliciting an immune response in an animal by consumption of the plant material."**

Arntzen et al. pays lip service to raising an immune response by ingestion, but in fact give no examples or teachings for obtaining such a result. **The only actual plant examples in Arntzen et al. relate to tomatoes and tobacco. There is no example of ingestion of either one and certainly no example showing that ingestion of either raises an immune response.** In fact, ingestion of the transgenic tomato does not raise any significant immune response (see the enclosed Rule 132 Declaration of Dr. Yasmin Thanavala) and certainly tobacco cannot be used for such a purpose because it is toxic. **Since there is no teaching in Arntzen et al. of how oral immunization to anything might be accomplished using a transgenic plant, and in fact the plants made in the examples do not function orally to raise an immune response, as Arntzen et al. alleges, it is clear that there is insufficient teaching or suggestion in Arntzen et al. to support a rejection of the present claims** whether the reference is considered alone or in combination with the other cited references. Arntzen certainly does not suggest that a potato expressing a NEPA could raise a secondary immune response when fed subsequent to immunization by injection, as presently claimed.

Simply making an unsupported allegation in a reference without a teaching as to how the allegation might be accomplished, is not a sufficient teaching to make a method for accomplishing the desired result obvious to one skilled in the art. Prophetic statements cannot be used to form the basis of a rejection, especially when they are unsupported and not true.

Arntzen et al. itself teaches and recognize that not all antigens would cause an immune response if ingested.

Arntzen et al. says in column 15 beginning at line 27,

"The vaccines are conventionally administered parentally, by injection, for example either subcutanously or intramuscularly. Additional formulations which are suitable for other modes of administration include suppositories and, ***in some cases***, oral formulations or aerosols." (emphasis added).

But there is no teaching or suggestion in Arntzen et al. of how the "some cases" could be determined or how the "some cases" could be accomplished.

While Arntzen et al. suggest that tomato juice containing HBsAg **might** be used as a vaccine, in fact Arntzen provides no supporting data showing any immune response whatsoever to tomato juice or any other plant containing HBsAg. To the extent that Arntzen teaches that tomato juice or any other plant material containing HBsAg can be used as a vaccine, it is an inoperative reference since there is no teaching or suggestion as to how that might be done. ***Simply ingesting the plant material, as suggested by Arntzen et al., does not confer immunity.***

There is good reason for Arntzen's omission of data showing a boosting immune response to HBsAg by ingesting food material containing it, since prior to the present invention, in fact, there was essentially no immune response to HBsAg in orally ingested tomato juice or any other plant expressing HBsAg. See the enclosed Rule 132 Declaration of Dr. Thanavala. The response, if any, is clearly insufficient for that purpose.

Reference to the examples in the present specification clearly illustrates that priming of the subject of the immunization is required by either pre-vaccination or the use of an effective adjuvant. Arntzen et al. suggests neither. **Arntzen et al. simply does not suggest preimmunization by injection followed by oral feeding of a transgenic potato expressing a NEPA to obtain a secondary immune response as required by the present claims whether or not Arntzen et al is combined with the other cited references.**

Arntzen's suggestion of simple ingestion of plant material expressing HBsAg does not give a sufficient immune response to be considered protective. Arntzen discloses or suggests no way in which a high immune response could be orally obtained and the other cited references do not remedy that critical defect as previously discussed.

The amendments made herein were necessary since they were made at the suggestion of the Examiner, to cancel duplicate or unnecessary claims, to narrow claims or to make the claims clearer. The amendments were not made earlier since the need for them was not recognized until the comments of the Examiner were received in the most recent official action. **In view of the new ground of rejection under 35 U.S.C. 112 first paragraph, which was not necessitated by any amendment made by the Applicants, it is requested that the finality of the rejection be withdrawn and that a new official action be provided.**

In view of the foregoing amendments and remarks, it is courteously requested that all rejections be withdrawn and all claims be allowed.

Respectfully submitted,

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Enclosures
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